PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference C2521-PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/08355	International filing date *(day/month/year)* 28.07.2003	Priority date *(day/month/year)* 31.07.2002
International Patent Classification (IPC) or both national classification and IPC C07K16/42		
Applicant D. COLLEN RESEARCH FOUNDATION VZW		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1-3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26.01.2004	21.09.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized Officer Mateo Rosell, A.M. Telephone No. +49 30 25901-319

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/08365

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-39 as originally filed

Claims, Numbers

1-16 filed with telefax on 16.07.2004

Drawings, Sheets

1/10-10/10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 11-14

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-5,7-10,15,16
	No:	Claims	1,2,6
Inventive step (IS)	Yes:	Claims	3-5,7-10,15,16
	No:	Claims	1,2,6
Industrial applicability (IA)	Yes:	Claims	1-10,15-16
	No:	Claims	11-14 (no opinion)

2. Citations and explanations

see separate sheet

Re Item I
Basis of the opinion

Reference is made to the following documents:

D1; Gilles et al., 1999. Blood, 94 (suppl.10, part 1), page 460a : abstract 2048.
D2: Genebank accession number: AAW27416 corresponding to the international application WO9710354 (Kyowa Hakko Kogyo KK). 20-03.1997;
D3: Genebank accession number: AAR52526 corresponding to the European application EP592106 (Immunogen Inc.) 13-04-1994;
D4: Genebank accession number: AX417628 corresponding to the international application number WO2331510 (PEPSCCAN SYSTEMS BV) 18.06.2002.
D5: Genebank accession number: AR144014 corresponding to the U.S. application US6210671 (Protein Design Labs, Inc.) 03-04-2001;
D6: Genebank accession number: AAT38510 corresponding to the international application WO9632495 (LG Chem. Ltd.) 06-04-1996.

The documents D2-D6 were not cited in the international search report.

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 11-14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Novelty

The present application does not meet the requirements of Article 33(1) PCT, because the subject-matter of claims 1,2 and 6 is not new in the sense of Article 33(2) PCT.

D2 discloses (see abstract) the CDR2 from the heavy chain variable region of KM1259

antibody which is 17 aa long and shows a 93.3% identity in 15 aa overlap with SEQ.ID.N.5 from present application.
D3 discloses (see abstract) the CDR1 light chain from antibody 3D6 which is 11 aa long and shows 72.7% identity in 11 aa overlap with SEQ.ID.N.8 form present application.

D4 discloses (see abstract) a synthetic peptide derived from antibody 3hfm.pdb which is 10 aa long and shows 88.8% identity in 9 aa overlap with SEQ.ID.N.10 from present application.

(The attention of the Applicant is drawn to the fact that in a later European Phase, a non-unity objection could be raised against the peptides of independent claim 6).

D5 discloses (see abstract) the heavy chain coding sequence of humanized immunoglobulins specifically reactive with L-selectin (SEQ.ID.N.3: 420 aa in length) which shows 91.3% identity in 366 aa overlap with SEQ.ID.N.1 from present application.

D6 discloses (see abstract) the light chain coding sequence of monoclonal antibody 4-1BB (363 aa in length) which shows 87.1% identity in 363 aa overlap with SEQ.ID.N.3 from present application.

2. Inventive step

2.1. The problem to be solved by the present application can be regarded as the provision of pharmaceutical compositions for the treatment of haemophilia, specially for the treatment of human patients who have developed FVIII inhibitors directed to the C2 domain.

2.2. The problem is solved by the subject-matter of claims 2-5,7-16, which provide an anti-idiotypic antibody reactive with the C2 domain of FVIII and peptides derived thereof which bind to the C2 domain of FVIII.

The anti-idiotypic antibody from the present invention is characterized by its heavy chain (SEQ.ID.N.1) and light chain (SEQ.ID.N.3) and the CDR regions therein (CDR1-H1: SEQ.ID.N.5; CDR2-H2: SEQ.ID.N.6; CDR3-H3: SEQ.ID.N.7; CDR1-L1: SEQ.IDN.8; CDR2-L2: SEQ.ID.N.9 and CRD3-L3: SEQ.ID.N.10). The antibody presents the properties of neutralizing the FVIII inhibitors (at least 50% neutralization) and does not interfere with the binding of FVIII with vWF and phospholipids.

The results obtained (see specially examples 4 and 5) shows that the variable part of the heavy chain of the antibody from the present invention contains an internal image of C2 made of 13 identical or homologous amino acid residues (see page 29, lines 29-31) associated with the CDR regions clustering to the CDR1 and CDR3 (see page 30, lines 25-26).

2.3. The closest prior art is considered to be **D1** (see abstract) which discloses a monoclonal anti-idiotypic antibody against a human Factor VIII inhibitory antibody (LE2E9) from which the subject-matter of claim 1 differs in that the antibody is being directed against the C1 domain of Factor VIII.

Therefore, the subject-matter of claims 4-5,7-16 is considered to involve an inventive step in the sense of Art. 33(3) PCT.

3. Industrial applicability

For the assessment of the present **claims 11-14** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4. Other remarks

Art. 6 PCT

4.1. It is clear from the description on page 7, line 1 to page 8, line 10 that the following features are essential to the definition of the invention:

(1) a monoclonal (anti-idiotypic) antibody, (directed against the C2 domain of Factor VIII)
(2) wherein the variable heavy chain of this antibody is encoded by the nucleotide sequence depicted in SEQ.ID.N.1 or a nucleotide sequence having at least 70% sequence identity to SEQ.ID.N.1, **and** wherein the variable light chain of this antibody is encoded by the nucleotide sequence depicted in SEQ.ID.N.3 or a nucleotide sequence having at least 70% sequence identity to SEQ.ID.N.3

Since independent claim 1 does not contain these features it does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.

4.2. The antibody 14C12, claim 5, has to be defined in technical terms, i.e. sequence identity or as a deposited cell line in order to comply with Article 6 PCT taken in combination with Rule 6.3(b) PCT.

ID AAW27416 standard; peptide; 17 AA.
XX
AC AAW27416;
XX
DT 27-AUG-2003 (revised)
DT 19-DEC-1997 (first entry)
XX
DE CDR2 from heavy chain variable region of KM1259 antibody.
XX
KW Complementarity determining region; CDR; heavy chain; treatment;
KW variable region; murine; mouse; human; interleukin 5; IL-5; receptor;
KW alpha chain; monoclonal antibody; hybridoma; detection; assay; diagnosis;
KW allergic respiratory disease; chronic bronchitis.
XX
OS Mus sp.
XX
PN WO9710354-A1.
XX
PD 20-MAR-1997.
XX
PF 11-SEP-1996; 96WO-JP002588.
XX
PR 11-SEP-1995; 95JP-00232384.
XX
PA (KYOW) KYOWA HAKKO KOGYO KK.
XX
PI Koike M, Furuya A, Nakamura K, Iida A, Anazawa H, Hanai N;
PI Takatsu K;
XX
DR WPI; 1997-202249/18.
XX
PT Antibody against alpha-chain of human interleukin 5 receptor - useful for
PT diagnosis and treatment of respiratory allergic diseases, e.g. chronic
PT bronchitis.
XX
PS Claim 8; Page 164; 238pp; Japanese.
XX
CC The present sequence is complementarity determining region 2 (CDR2) from
CC the heavy chain variable region of the murine anti-human interleukin 5
CC receptor alpha chain (hIL-5R alpha) monoclonal antibody (MAb) KM1259.
CC KM1259 is produced by the hybridoma FERM BP-5134, which was prepared by
CC immunising Balb/c mice with hIL-5R alpha, fusing spleen cells obtained
CC from the mice with mouse myeloma P3-U1 cells and screening the resultant
CC hybridomas. The MAb can be used to detect or assay for hIL-5R alpha and
CC cells expressing it on their surface, especially to diagnose allergic
CC respiratory diseases, e.g. chronic bronchitis. It can also be used to
CC treat such diseases. (Updated on 27-AUG-2003 to correct OS field.)
XX
SQ Sequence 17 AA;
SQ 0 A; 1 R; 3 N; 1 D; 0 B; 0 C; 0 Q; 1 E; 0 Z; 2 G; 0 H;
SQ 1 I; 0 L; 2 K; 0 M; 1 F; 1 P; 0 S; 1 T; 0 W; 3 Y; 0 V;
SQ 0 Others;
yinpyndgtk ynerfkg
//

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ID   AAR52526 standard; peptide; 11 AA.
XX
AC   AAR52526;
XX
DT   10-OCT-1996  (first entry)
XX
DE   3D6 light chain complementarity determining region 1.
XX
KW   antibody; humanised; murine; human; heavy chain; light; variable;
KW   framework region; complementarity determining region; reshaping;
KW   modelling; surface residue; modify; anti-phenylarsonate antibody.
XX
OS   Synthetic.
XX
PN   EP592106-A1.
XX
PD   13-APR-1994.
XX
PF   07-SEP-1993;   93EP-00307051.
XX
PR   09-SEP-1992;   92US-00942245.
XX
PA   (IMMU-) IMMUNOGEN INC.
XX
PI   Pedersen JT,  Searle SMJ,  Rees AR,  Roguska MA,  Guild BC;
XX
DR   WPI; 1994-120230/15.
XX
PT   Method of resurfacing of rodent antibodies to produce humanised antibody
PT   forms - for producing non human antibodies with improved therapeutic
PT   efficiency by presenting human surface on V-region.
XX
PS   Example 2; Page 31; 230pp; English.
XX
CC   The predicted structures of 4 different antibody (Gloop-2 and D1.3, anti-
CC   lysozyme Abs; 36-71, an anti-phenylarsonate Ab; and 3D6, an anti- protein
CC   (GP41 of HIV) Ab) Fv regions were analysed. This information can be used
CC   in a method to determine how to modify a rodent antibody or fragment by
CC   resurfacing in order to produce a humanised rodent antibody. Global fits
CC   give a more realistic measure of the accuracy of the model than a local
CC   least-squares fit over the loops since they account for the overall
CC   positioning of the loops in the context of the Fv structure. Differences
CC   between local and global Root Mean Square deviations arise from
CC   differences in VH/VL domain packing and differences in loop "take off"
CC   angles and positions. AAR52523-46 are the peptide sequences of the 24
CC   CDRs
XX
SQ   Sequence 11 AA;
SQ   1 A; 1 R; 2 N; 0 D; 0 B; 0 C; 1 Q; 0 E; 0 Z; 1 G; 1 H;
SQ   1 I; 1 L; 0 K; 0 M; 0 F; 0 P; 2 S; 0 T; 0 W; 0 Y; 0 V;
SQ   0 Others;
     rasqsignnl h
//
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ID   AX417628   standard; PRT; 10 AA.
XX
AC   AX417628;
XX
SV   AX417628.1
XX
DT   18-JUN-2002 (Rel. 72, Created)
DT   18-JUN-2002 (Rel. 72, Last updated, Version 1)
XX
DE   Sequence 51 from Patent WO0231510.
XX
KW   .
XX
OS   synthetic construct
OC   artificial sequences.
XX
RN   [1]
RA   Meloen R.H., Puijk W.C., van Dijken P., van Dijk E.;
RT   "Identification of protein binding sites";
RL   Patent number WO0231510-A/51, 18-APR-2002.
RL   PEPSCAN SYSTEMS B V (NL).
XX
FH   Key             Location/Qualifiers
FH
FT   source          1..10
FT                   /db_xref="taxon:32630"
FT                   /note="synthetic peptide derived from antibody 3hfm.pdb"
FT                   /organism="synthetic construct"
XX
SQ   Sequence 10 AA; 1239 MW; 1D37866E CRC32;
     QQSNSWPYTE
//
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gtaatgttg gagtgtacta ctgtcaagat ggtcacagct ttcctccgac gttcggtgga      300
gtcaccaagc tggaaatcaa acgcgctgat gctgcaccaa ctgtatccat cttccaccga      360
tcc                                                                    363
```

ID AR144014 standard; unassigned DNA; UNC; 420 BP.
XX
AC AR144014;
XX
SV AR144014.1
XX
DT 09-AUG-2001 (Rel. 68, Created)
DT 09-AUG-2001 (Rel. 68, Last updated, Version 1)
XX
DE Sequence 3 from patent US 6210671.
XX
KW .
XX
OS unidentified
OC unclassified.
XX
RN [1]
RP 1-420
RA Co M.Sung.;
RT "Humanized antibodies reactive with L-selectin";
RL Patent number US6210671-A/3, 03-APR-2001.
XX
DR IMGT/LIGM; AR144014; AR144014.
XX
FH Key   Location/Qualifiers
FH
FT source   1..420
FT   /db_xref="taxon:32644"
FT   /mol_type="unassigned DNA"
FT   /organism="unidentified"
XX
SQ Sequence 420 BP; 101 A; 98 C; 115 G; 106 T; 0 other;
     atggaatgga gttggatatt tctctttctc ctgtcaggaa ctgcaggtgt ccactctgag 60
     gtccagctgc agcagtctgg acctgacctg gtaaagcctg gggcttcagt gaagatgtcc 120
     tgcaaggctt ctggatacac attcactagc tatgttatgc actgggtgaa gcagaagcct 180
     gggcagggcc ttgagtggat tggatatatt tatccttaca atgatggtac taagtacaat 240
     gagaagttca aaggcaaggc cacactgact tcagacaaat cctccagcac agcctacatg 300
     gagctcagca gcttgacctc tgaggactct gcggtctatt actgtgcaag ggaggagtat 360
     ggtaactacg ttcggtactt cgatgtctgg ggcgcaggga ccacggtcac cgtctcctca 420
//

Amended claims for PCT/EP2003/008365

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1. A monoclonal anti-idiotypic antibody against a human Factor VIII inhibitory antibody, the said inhibitory antibody being directed towards the C2 domain of Factor VIII, characterized by the fact that a complementary determining region of the variable heavy chains of said anti-idiotypic antibody has at least 70 % sequence identity to one of the amino acid sequences depicted in SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO:7 or a complementary determining region of the variable light chains of said anti-idiotypic antibody has at least 70 % sequence identity to one of the amino acid sequences depicted in SEQ ID NO:8 SEQ ID NO:9 and SEQ ID NO:10.

2. The monoclonal anti-idiotypic antibody according to claim 1, against the C2 domain of FVIII wherein the variable heavy chain of the said anti-idiotypic antibody is encoded by the nucleotide sequence depicted in SEQ ID NO 1 or a nucleotide sequence having at least 70% sequence identity to SEQ ID NO 1 and/or wherein the variable light chain of the anti-idiotypic antibody is encoded by the nucleotide sequence depicted in SEQ ID NO 3 or a nucleotide sequence having at least 70% sequence identity with SEQ ID NO 3.

3. The monoclonal anti-idiotypic antibody according to any of claims 1 or 2, which is an F(Ab')2 fragment, an Fab' fragment , an Fab fragment or a modified version of said fragment.

4. The monoclonal anti-idiotypic antibody according to any of claims 1 to 3, which is a humanized monoclonal anti-idiotypic antibody.

5. The monoclonal anti-idiotypic antibody according to any of claims 1 to 4, which is 14C12 or an antibody derived therefrom.

6. An isolated and purified peptide capable of binding to an antibody directed against the C2 domain of factor VIII, said peptide comprising an amino acid sequence selected from SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9 and SEQ ID NO:10 or a sequence which is at least 70 % identical in amino acid sequence selected from SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9 and SEQ ID NO:10.

7. A monoclonal cell line expressing a monoclonal anti-idiotypic antibody in accordance with any of claims 1 to 6.

8. cell line in accordance with claim 7, which is the cell line 14C12 deposited at BCCM with Accession Number LMBP 5878CB.

9. A pharmaceutical composition comprising a monoclonal anti-idiotypic antibody according to any of claims 1 to 5, or an isolated and purified peptide according to claim 6, in admixture with at least one pharmaceutically acceptable carrier.

10. Use of a monoclonal anti-idiotypic antibody according to any one of claims 1 to 5 or an isolated and purified peptide according to claim 6 as a medicine.

11. A method of treating patients suffering from the effects of FVIII inhibitory antibodies, said method comprising, administering to said patient a therapeutically effective dose of the pharmaceutical composition according to claim 9.

12. A method of treatment or prevention of uncontrolled bleeding in a patient with FVIII inhibitory antibodies, said method comprising administering to said patient a therapeutically effective dose of the pharmaceutical composition according to claim 9.

13. The method according to claim 12, which further comprises administering to said patient FVIII.

14. The method of any one of clams 11 to 13, wherein said patient is a haemophiliac.

15. A method for developing monoclonal anti-idiotypic antibodies for the manufacture of a medicament against FVIII inhibitors, said method comprising immunizing an animal with inhibitory antibodies directed against the C2 domain of FVIII and screening the immortalized spleen cells of said animal for the production of antibodies which a) neutralise the anti-coagulant activity of FVIII inhibitors for at least 50% and b) do not interact with the binding of FVIII to vWF and phospholipids.

16. The use of the anti-idiotypic antibodies of any one of claims 1 to 5 for the detection or purification of inhibitory FVIII antibodies.